C2 Rob D2

4. (THREE TIMES AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more monoclonal antibodies which specifically compete for binding to cervical cells with one or more antibodies obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

C3 Rob D3

8. (TWICE AMENDED) A specific monoclonal antibody which specifically competes for binding to cervical tissue with a monoclonal antibody according to claim 7.

Remarks

Claims 1-5 and 7-8 are pending. Claims 1, 3, 4 and 8 have been amended. Support for the amendments is found throughout the specification, for example at p. 1, line 7; p.28, lines 19-20; p. 4, lines 16-17; p. 15, line 25 to p.16, line2; p. 9, lines 5-7; and Tables 1 and 2.

Allowable claims

The Examiner has indicated that claims 5 and 7 are allowable.

Rejection under 35 U.S.C. § 102(b)

Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as being anticipated by any of Porta et al. (*Pat. Clin. Ost. Gin.*, 14:348-55 (1986), "Porta"), Kamiya et al. (*Acta Cytologica*, 37:131-34 (1993), "Kamiya"), or Smedts et al. (*Amer. J. Pathol.*, 142:403-12 (1993), "Smedts").

Claims 1 and 2 are directed at methods of screening for a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix. The method comprises contacting a panel of two or more monoclonal antibodies with said sample, each antibody being raised against a different antigen within the same sample, and then determining the binding pattern of the monoclonal antibodies to the sample. The binding pattern is then compared to the binding pattern of the monoclonal antibodies to a normal cervical cell sample. The

monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

"Anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference... There must be no difference between the claimed invention and the referenced disclosure, as viewed by a person of ordinary skill in the field of invention." Scripps Clinic and Research Foundation v. Genentech, Inc., 18 USPQ 2d 1001.

Porta generally teaches the use of monoclonal antibodies in immunohistological techniques as a means of identifying abnormal patterns of antigen expression in neoplastic cervical epithelium for diagnosis and prognosis. The Examiner argues that Porta teaches contacting cervical epithelium with "monoclonal antibodies" and that the plural term indicates a "panel of two or more" antibodies. Applicants disagree.

The plural term in Porta is used in a general sense and does not indicate that two or more antibodies are used on the same cervical smear sample, as in the present claims. Rather, it suggests that more than one monoclonal antibody is known and each may have value as an indicator. Porta clearly does not teach the use of a "panel" of antibodies to analyze a given cervical smear sample, and therefore does not anticipate the claims.

Kamiya teaches detection of cervical small cell undifferentiated carcinoma comprising staining samples of cervical carcinoma cells with monoclonal antibodies against cluster 1 small cell lung cancer antigen and comparing the staining pattern to non-small cell cervical cancers. Kamiya does not teach a method wherein the monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells. Rather, Kamiya only compares binding between squamous cell carcinoma and adenocarcinoma, with the apparent intent to diagnose a particular type of carcinoma. The present claims, however, cover methods that distinguish normal from abnormal cells of the cervix.

Additionally, Kamiya does not disclose or suggest a method wherein a panel of at least two monoclonal antibodies having different antigen specificities is used. Instead, Kamiya uses one of three possible antibodies with all of these antibodies being raised against the same

antigen. The antigen in question is cluster 1 small cell lung cancer antigen which is not an antigen of a cervical cell. Thus, Kamiya does not teach the claimed invention.

Smedts teaches determination of cervical neoplasia and carcinoma comprising determining the binding of monoclonal antibodies directed against specific keratins to cervical tissues and comparing the pattern of expression of the keratins in the sample with the patterns of expression in normal and malignant cells. Smedts is primarily concerned with determining several keratins' expression patterns across a range of normal, premalignant and malignant cell types.

The Examiner argues that Smedts teaches contacting cervical tissue samples with a panel of 5 monoclonal antibodies. The claims as amended are drawn to methods of screening a cervical smear sample. Tissue samples, as used by Smedts, are coherent portions of tissues which have kept their original structure and wherein cells have kept their natural relationship. Cervical smear samples, by contrast, are merely a collection of cells. Cervical smear samples have not retained the relationship or structure of the original tissue. Smedts' methods did not utilize cervical smears.

Additionally, the results of Smedts's study does not demonstrate a "marker" that differs between premalignant or neoplastic cells. Smedts shows that columnar epithelium may be distinguished from ectocervical epithelium; that various grades of cervical intraepithelial neoplasias (CINs) can be distinguished from each other (i.e., CIN I and CIN II from CIN III); that keratinizing squamous cell carcinoma may be distinguished from non keratinizing carcinoma; and that the adenocarcinoma keratin phenotype is related to that of squamous cell carcinoma. (*See* p. 411). Smedts notes the "complexity" and variability of keratin expression in the cell types studied. (*See* p. 403, Abstract, and p.411). Smedts does not teach or suggest distinguishing normal cervical cells from premalignant or neoplastic cervical cells.

Kerr, Porta, Kamiya and Smedts do not teach the method comprising contacting two or more monoclonal antibodies with a cervical smear sample, determining binding to the sample and comparing binding with the binding to a normal cervical cell sample, wherein the antibodies detect markers which differ between normal and premalignant or neoplastic cells.

Since the references do not teach each and every limitation of Claim 1, they do not anticipate Claim 1 under 35 U.S.C. § 102. Applicants respectfully request the Examiner to withdraw this rejection.

Rejections under 35 U.S.C. § 102/103

Claim 8 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over any of Kerr, Porta, Kamiya, or Smedts.

Claim 8 has been amended to recite that the specific antibody "specifically competes" with a monoclonal antibody according to claim 7. Thus, non-specific binding mechanisms are not encompassed by the claims. Applicants respectfully submit that claim 8 as amended is allowable and request that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph (Enablement)

Claims 1-4 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

Enablement under 35 U.S.C. § 112 requires that the disclosure contain sufficient information to enable one skilled in the art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement is whether any person skilled in the art can make and use the invention without undue experimentation. *See* MPEP 2164.01. *In re Wands* describes several factors to consider in determining whether any necessary experimentation is "undue." *See* MPEP 2164.01(a).

The Examiner has based the rejection on the analysis of several of the *In re Wands* factors. However, the Examiner has not first demonstrated that experimentation would be required to make and use the invention. Applicants submit that the invention is fully enabled and that no experimentation is required to make and use the invention.

The Examiner argues that the art teaches that normal cervical cells also express antigens expressed in premalignant or neoplastic cells. However, the Examiner fails to recognize that the present invention uniquely identifies and uses antibodies that differ in their binding patterns between normal and disease cells. (*See* p. 3, lines 9-19; p. 4, lines 15-28; Example 5).

The Examiner further argues that antigens expressed in premalignant and neoplastic cells differ according to the type of disease and thus cellular antigens expressed in one type of neoplasia are not necessarily expressed in others. Applicants submit that the invention is not aimed at distinguishing different types of neoplasia; rather, the claimed method detects an abnormal pattern of binding of a panel of monoclonal antibodies, indicative of a premalignant or neoplastic disease state. Example 5 in particular demonstrates that the binding pattern of the panel of antibodies detects differences between normal and CIN cells. Additionally, the specification states, "Diagnosis and decisions on the need for and nature of treatment remain the domain of clinicians." (Page 3, line 27 to page 4 line 1).

The Examiner states that there is no specific group of specific cellular markers that is in and of itself diagnostic of a premalignant or neoplastic condition. Additionally, the Examiner argues that expression of markers is at best used in conjunction with other parameters in determining the presence of a premalignant or neoplastic condition. Applicants submit that the examples demonstrate a group of monoclonal antibodies that react differently with normal and abnormal cervical cells. The claimed method does not rely on correlation of other parameters. Rather, the method utilizes a combination of antibodies with a characteristic binding pattern against normal cervical cells. A binding pattern that deviates from the normal pattern signals a particular abnormality in the cervical smear sample examined. Identification of the particular abnormality and diagnosis are not required by the invention; rather, the invention allows abnormal samples to be identified for further examination. Some of the so identified samples will be premalignant or neoplastic.

The Examiner also argues that additional guidance is required because diagnosis cannot be based solely on the pattern of cellular markers, but requires further examination of individual samples. The Examiner states undue experimentation would be required to practice the claimed invention. Applicants disagree. Applicants claim methods of determining a premalignant or neoplastic disease state by correlating the expression of marker antigens. The language of the specification to which the Examiner refers (page 48, lines 16-21) does not suggest a lack of enablement. Rather, the specification states that the information obtained

from practicing the invention can be used to identify samples which require further examination. Methods of clinical diagnosis are not specifically set forth in the claims. (*See* specification at page 3, line 14 to page 4, line 1).

Conclusion

Applicants submit that the claims are now in condition for allowance and an early notification of such is solicited. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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MARKED UP VERSION TO SHOW CHANGES MADE

1. (TWICE AMENDED) A method of [determining] screening for a premalignant or neoplastic disease state in a [tissue] cervical smear sample containing cells of the cervix, the method comprising contacting a panel of two or more monoclonal antibodies with said [tissue] sample, each antibody having specificity for a different antigen of said sample relative to the other antibodies in said sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

3. (TWICE AMENDED) A method of determining a premalignant or neoplastic disease state in a [tissue] cervical smear sample containing cells of the cervix, the method comprising contacting one or more monoclonal antibodies with said [tissue] sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells and wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

4. (THREE TIMES AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more monoclonal antibodies which specifically compete for binding to cervical [tissue] cells with one or more antibodies obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (TWICE AMENDED) A specific monoclonal antibody which specifically competes for binding to cervical tissue with a monoclonal antibody according to claim 7.

National Phase Entry of
International Application No.:
PCT/GB97/02108 which was filed:
August 5, 1997

APPENDIX OF CLAIMS:

1. (TWICE AMENDED) A method of screening for a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting a panel of two or more monoclonal antibodies with said sample, each antibody having specificity for a different antigen of said sample relative to the other antibodies in said sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells.

2. (AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain.

3. (TWICE AMENDED) A method of determining a premalignant or neoplastic disease state in a cervical smear sample containing cells of the cervix, the method comprising contacting one or more monoclonal antibodies with said sample, determining binding of said monoclonal antibodies to said sample and comparing the binding with a pattern of binding of said monoclonal antibodies to a normal cervical cell sample, wherein said monoclonal antibodies detect cellular markers which differ between normal and premalignant or neoplastic cells and wherein the monoclonal antibodies comprise one or more polypeptides each comprising an antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

4. (THREE TIMES AMENDED) A method according to claim 1 wherein the monoclonal antibodies comprise one or more monoclonal antibodies which specifically compete for binding to cervical cells with one or more antibodies obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

5. (AMENDED) (ALLOWED) A hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

7. (AMENDED) (ALLOWED) A specific monoclonal antibody comprising an immunoglobulin antigen binding domain obtained from a hybridoma selected from those deposited at the European Collection of Animal Cell Cultures (ECACC), under the accession numbers ECACC 95020718, ECACC 95020716, ECACC 95020720, ECACC 95020717 and ECACC 95020719.

8. (TWICE AMENDED) A specific monoclonal antibody which specifically competes for binding to cervical tissue with a monoclonal antibody according to claim 7.